# Summary of Safety and Effectiveness Data

## I. General Information

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|---|---|
| Device Generic Name: | A solid-phase chemiluminescent enzyme immunoassay for the qualitative detection of hepatitis B surface antigen (HBsAg) |
| Device Trade Name: | IMMULITE® HBsAg<br>IMMULITE® 2000 HBsAg<br>IMMULITE® HBsAg Confirmatory Kit |
| Applicant's Name and Address: | Diagnostic Products Corporation<br>5700 West 96th Street<br>Los Angeles, California 90045-5597 |

Premarket Approval Application (PMA) Number: P010050

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: July 26, 2002

## II. INDICATIONS FOR USE

### IMMULITE HBsAg

IMMULITE HBsAg is a solid-phase chemiluminescent enzyme immunoassay designed for use on the IMMULITE automated immunoassay analyzer for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum or plasma (EDTA, heparin, citrate). It is intended for in vitro diagnostic use for the laboratory diagnosis of acute and chronic hepatitis B virus infections in conjunction with other serological and clinical information. In addition, this assay may be used to screen for hepatitis B infection in pregnant women to identify neonates who are at high risk of acquiring HBV during the perinatal period.

### IMMULITE 2000 HBsAg

IMMULITE 2000 HBsAg is a solid-phase chemiluminescent enzyme immunoassay designed for use on the IMMULITE 2000 automated immunoassay analyzer for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum or plasma (EDTA, heparin, citrate). It is intended for in vitro diagnostic use for the laboratory diagnosis of acute and chronic hepatitis B virus infections in conjunction with other serological and clinical information. In addition, this assay may be used to screen for hepatitis B infection in pregnant women to identify neonates who are at high risk of acquiring HBV during the perinatal period.

**IMMULITE HBsAg Confirmatory**

IMMULITE HBsAg Confirmatory is intended for in vitro diagnostic use in conjunction with the IMMULITE HBsAg or the IMMULITE 2000 HBsAg assays for the confirmation of the presence of hepatitis B surface antigen (HBsAg) in human serum or plasma (EDTA, heparin, citrate) that was repeatedly positive when tested by IMMULITE or IMMULITE 2000 HBsAg.

## III. DESCRIPTION OF DEVICE

IMMULITE and IMMULITE 2000 HBsAg kits and the IMMULITE HBsAg Confirmatory Kit are the subjects of this PMA. The data and information are presented separately for all three.

The IMMULITE and IMMULITE 2000 HBsAg kits are solid phase, two step chemiluminescent enzyme immunoassays designed for use on the automated IMMULITE and IMMULITE 2000 analyzers, for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum or plasma. The kits are intended for in vitro use as an aid in the laboratory diagnosis of acute and chronic hepatitis B virus infections. The kits' solid phase is a polystyrene bead coated with an antibody directed against the hepatitis B surface antigen (anti-HBs). The patient sample and a protein-based buffer are simultaneously introduced into the Test Unit and incubated for approximately 30 minutes at 37 $^{o}$C with intermittent agitation. During this time, HBsAg in the patient sample binds to the anti-HBs coated bead. Unbound serum is then removed by a centrifugal wash. An alkaline phosphatase-labeled anti-HBs is introduced, and the reaction tube is incubated with agitation for another 30 minute cycle. The unbound enzyme conjugate is removed by a centrifugal wash. After the wash, a chemiluminescent substrate is added, and the reaction tube is incubated with agitation for a further 5 – 10 minutes.

The chemiluminescent substrate is a phosphate ester of adamantyl dioxetane which undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The bound complex and the resulting photon output, measured as cps by the photomultiplier tube, is related to the presence of HBsAg in the sample. A qualitative result is then obtained by comparing the patient results to an established cutoff.

In assays for HBsAg where the instrument response signal is directly related to the antigen concentration, the presence of HBsAg in a sample can be confirmed by demonstrating a significant reduction in signal following specific antibody neutralization. The signal reduction reflects a reduction in binding of HBsAg to the solid phase antibodies in the presence of blocking antibodies. A sufficiently decreased signal relative to that of a control sample confirms a positive HBsAg result.

The IMMULITE HBsAg Confirmatory kit is used in conjunction with the IMMULITE and IMMULITE 2000 HBsAg assays to confirm the presence of HBsAg in a patient

sample that has initially tested reactive for the antigen. In the confirmatory procedure, an undiluted sample and a 1:500 dilution of the sample are each divided into two aliquots. One aliquot is combined with a blocking reagent containing goat anti-HBs, the other with a control reagent which lacks the antibody.
For suitably diluted HBsAg positive samples, in the aliquots containing the blocking reagent, most of the HBsAg present in solution binds to the blocking antibody and does not bind to the coated bead; whereas, in the aliquots containing the control reagent, any HBsAg present in the sample remains free to bind to the coated bead. The original patient sample is confirmed positive for the presence of HBsAg if the signal from either the undiluted or diluted aliquots of the blocked aliquots is at least 50% less than the signal from the corresponding unblocked (control) aliquot.

## IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

There are no known contraindications for the IMMULITE HBsAg, IMMULITE 2000 HBsAg and the IMMULITE HBsAg Confirmatory Kit

Warning and precautions for users of the IMMULITE® HBsAg, IMMULITE®2000 HBsAg and the IMMULITE HBsAg Confirmatory assays are stated in the product labeling.

## V. ALTERNATIVE PRACTICES OR PROCEDURES

There are currently a variety of commercially available, FDA licensed or approved serological tests for the detection of HBsAg. Assays have been developed using radioimmunoassay or enzyme immunoassay methodologies. When the test results are used in combination with other serological markers expressed during the three phases of incubation, the presence of hepatitis B virus may be determined.

## VI. MARKETING HISTORY

IMMULITE HBsAg and IMMULITE 2000 HBsAg have been marketed internationally as an aid in the determination of hepatitis B virus infection status since July 1996. IMMULITE and IMMULITE 2000 HBsAg have received European Union CE Mark approval and have been marketed in Europe since June 2001.

## VII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

There are no direct adverse effects on the health of the patient if the devices are used according to the instructions in the package insert. However, failure of the device to perform as indicated or human error in use of the device may lead to inaccurate results and a misdiagnosis. A false positive result using an HBsAg assay may be considered a patient or public health concern if the positive result is not done in a clinical lab setting where a positive test is followed up with supplemental testing. Either additional HBV marker testing is performed or an HBsAg positive result is confirmed by neutralization. An exception to this is using HBsAg tests to screen pregnant women for the presence of

HBsAg. This testing helps to determine if a neonate is at high risk of acquiring HBV during the prenatal period. Pregnant women are tested during an early prenatal visit. If they are HBsAg nonreactive during this testing, and at high risk for HBV infection, they are re-tested during the third trimester. If the result is positive, it is recommended that hepatitis B immune globulin (HBIG) and vaccine be provided to the newborn within 12 hours of birth. If an assay is false positive and the newborn receives HBIG, the new born would be exposed to the risks of receiving a human source product.
The risks of a false negative result in a diagnostic setting are highest when testing pregnant women because HBsAg may be the only marker used. If the result is negative then the child is vaccinated within 2 months of birth. If the result is incorrect (false negative), the neonate is at a higher risk of acute and chronic HBV infection, since HBIG and vaccine would not be provided within 12 hours of birth.

In addition, from time to time false negative results due to gene mutation have been reported for HBsAg assays produced by a number of different manufacturers. Because of the complexity of the mutations that can occur, no manufacturer can guarantee to detect all infectious donors and patients.

A false positive result using an HBsAg confirmatory neutralization procedure is not considered a patient or public health concern because in order for a false positive to occur, the control sample (non-neutralized result) and the percent neutralization (in neutralized tube) would both have to be incorrect for a reported false positive result. If this situation were to occur, the implications would be the same as described for false positive results for HBsAg assays.

A false negative result using an HBsAg confirmatory neutralization procedure could occur if the neutralized sample were incorrect either due to a falsely increased signal with the neutralized sample, or due to some other malfunction, laboratory or technician error when assayed. A falsely increased signal could be interpreted as a failure to neutralize. If this situation were to occur, the implications would be the same as described for false negative results for HBsAg.

## VIII. SUMMARY OF NON CLINICAL STUDIES

### Analytical Specificity

Analytical specificity was evaluated at two clinical sites in the United States and at one European site. In the United States, serum specimens from 17 subgroups of patients with potentially cross-reacting microorganisms or conditions were tested by IMMULITE HBsAg and a commercially available enzyme immunoassay for HBsAg (Kit A). These results are listed in the package insert.

In the European study, eight specimens from antinuclear antibody (ANA) positive patients and 30 from patients with positive rheumatoid factor (RF) were tested by IMMULITE HBsAg. IMMULITE HBsAg test results were all negative for these 38 specimens.

The specimens were also tested by IMMULITE 2000 HBsAg, at the same sites. The test results are presented in the package inserts.

In the European study, seven specimens from antinuclear antibody (ANA) positive patients and 24 from patients with positive rheumatoid factor (RF) were tested by IMMULITE 2000 HBsAg. IMMULITE 2000 HBsAg test results were all negative for these 31 specimens.

**Analytical Sensitivity**

Based on studies with serial dilution of WHO International Standard for Hepatitis B Surface Antigen (NIBSC 80/549), the threshold sensitivity (last positive dilution) for IMMULITE and IMMULITE 2000 HBsAg is 0.063 IU/mL. The 95% confidence interval at this level (0.063 IU/mL) is 0.040 - 0.086 IU/mL.

**Effects of Bilirubin, Lipemia and Hemolysis**

To simulate moderate and severe icterus, different volumes of each of 6 patient samples ranging from very negative to high positive hepatitis B surface antigen values were pipetted into lyophilized unconjugated bilirubin to achieve 3 levels of bilirubin concentrations (10 and 20 mg/dL) for each sample. The spiked and unspiked samples were assayed by the IMMULITE and IMMULITE 2000 HBsAg assays. In the IMMULITE HBsAg tests, the spiked samples had averages of 96%, 99% and 99% recovery for all samples for 10 and 20 mg/dL of bilirubin concentrations, respectively. In the IMMULITE 2000 HBsAg tests, the spiked samples had averages of 101%, 98% and 101% recovery for all samples for 10 and 20 mg/dL bilirubin concentrations, respectively. This study demonstrated that the measurement of hepatitis B surface antigen was not affected by the presence of bilirubin up to 20 mg/dL.

To simulate mild, moderate and severe hemolysis, the same 6 samples were spiked with hemolysate to achieve final hemoglobin levels of 168, 252 and 504 mg/dL. The samples were assayed, both spiked and unspiked, by the IMMULITE and IMMULITE 2000 HBsAg assays. Expected kCPS for each sample was calculated based on the spiking factor and compared with the observed kCPS. In the IMMULITE HBsAg tests, the spiked samples had averages of 115%, 126% and 144% recovery for all samples for 168, 252 and 504 mg/dL hemoglobin concentrations, respectively. In the IMMULITE 2000 HBsAg tests, the spiked samples had averages of 111%, 114% and 136% recovery for all samples for 168, 252 and 504 mg/dL hemoglobin concentrations, respectively. Since increases of responses (kcps) were observed in the spiked samples (especially the low samples) with the increase of hemoglobin, it was concluded that the measurement of hepatitis B surface antigen may be affected by the presence of red blood cells. The results of hemolyzed samples should be interpreted with caution.

The same 6 samples were each spiked with 4 levels of triglycerides at 500, 1000, 2000 and 3000 mg/dL to evaluate the lipemia effect on the IMMULITE and IMMULITE 2000 HBsAg assays. Unspiked and spiked samples were tested by the IMMULITE and IMMULITE 2000 HBsAg assays. Since increases of responses (kcps) in the spiked

samples correlated with the increase of triglyceride levels, it was concluded that the measurement of hepatitis surface antigen may be affected by the presence of triglycerides. The use of an ultracentrifuge is recommended to clear lipemic samples.

**Hook Effect and Carryover**

The hook effect study demonstrated that the IMMULITE and IMMULITE 2000 HBsAg assays did not have a hook effect up to at least 2000 times the titer of the cutoff.

The carryover study demonstrated that the IMMULITE and IMMULITE 2000 HBsAg assays did not exhibit a carryover phenomenon when samples were preceded by a sample with very high antigen titers.

**Interfering Substances**

A study was conducted to evaluate the effects of interfering substances on IMMULITE and IMMULITE 2000 HBsAg assays. Potential interfering substances that included common serum constituents, chemotherapeutic and other drugs were spiked into serum samples with 5 or 6 different levels of HBsAg. Listed below are the substances and their test levels (concentration).

| Interferring Substance | Concentration |
|---|---|
| HUMAN ALBUMIN | 6 g/dL |
| ASCORBIC ACID | 3 mg/dL |
| ALT | 7000 U/L |
| AST | 7000 U/L |
| ALK PHOSPHATASE | 5000 U/L |
| CORTISONE | 400 ug/dL |
| CYCLOSPORIN A | 18.02 ug/dL |
| GANCICLOVIR | 11.8 ug/mL |
| ETHANOL | 350 mg/dL |
| INTRON A | 2730 IU/mL |
| LAMIVUDINE | 20 ug/mL |
| LDH | 6000 U/L |
| NELFINAVIR | 40 ug/mL |

This study demonstrated that the detection of hepatitis B surface antigen by IMMULITE and IMMULITE 2000 HBsAg was not affected by the presence of any of the interfering substances listed up to the levels tested.

**Effects of Anticoagulants**

The measurement of HBsAg is not affected by the presence of heparin, sodium citrate, and EDTA anti-coagulants, as shown in a study that included 60 specimens collected into plain, heparinized, sodium citrate, and EDTA vacutainer tubes. By regression:

IMMULITE HBsAg (ratio):

(EDTA) = 1.01 (Serum) + 0.41 r = 1.00

(Na Citrate) = 1.03 (Serum) + 0.74 r = 1.00

(Heparin) = 1.03 (Serum) + 1.10 r = 1.00

IMMULITE 2000 HBsAg (ratio):

(EDTA) = 0.98 (Serum) + 1.52 r = 1.00

(Na Citrate) = 0.96 (Serum) + 0.83 r = 1.00

(Heparin) = 0.99 (Serum) + 1.93 r = 1.00

In another study conducted in the northwestern United States, blood samples from 18 chronic hepatitis B patients at different stages of the disease were drawn into plain tubes and blood collection tubes that contained Na citrate, EDTA or heparin. All samples were assayed by IMMULITE and IMMULITE 2000 HBsAg. Test results for serum samples and plasma samples were all consistent for all 18 patients, yielding 100% agreement between serum and the three anticoagulant samples for both assays.

**Precision**

Serum samples were assayed in duplicate over the course of 20 days, two runs per day, for a total of 40 runs and 80 replicates at three US sites.

IMMULITE HBsAg Intrassay and Total Precision (ratio)

Site 1

| | | Intra-assay | | Total | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.44 | 0.033 | 7.5% | 0.039 | 8.9% |
| 2 | 0.44 | 0.056 | 12.6% | 0.073 | 16.5% |
| 3 | 1.19 | 0.072 | 6.0% | 0.078 | 6.5% |
| 4 | 1.23 | 0.087 | 7.1% | 0.165 | 13.4% |
| 5 | 1.44 | 0.102 | 7.1% | 0.126 | 8.7% |
| 6 | 2.96 | 0.173 | 5.9% | 0.191 | 6.4% |

Site 2

| | | Intra-assay | | Total | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.41 | 0.043 | 10.5% | 0.051 | 12.2% |
| 2 | 0.42 | 0.059 | 14.1% | 0.079 | 18.9% |
| 3 | 1.18 | 0.067 | 5.7% | 0.118 | 10.0% |
| 4 | 1.20 | 0.059 | 4.9% | 0.156 | 13.0% |
| 5 | 1.37 | 0.059 | 4.3% | 0.180 | 13.1% |
| 6 | 2.86 | 0.163 | 5.7% | 0.356 | 12.5% |

Site 3

| | | Intra-assay | | Total | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.44 | 0.051 | 11.8% | 0.071 | 16.3% |
| 2 | 0.42 | 0.044 | 10.6% | 0.056 | 13.4% |
| 3 | 1.14 | 0.089 | 7.8% | 0.122 | 10.7% |
| 4 | 1.13 | 0.086 | 7.6% | 0.166 | 14.7% |
| 5 | 1.43 | 0.062 | 4.3% | 0.146 | 10.2% |
| 6 | 2.86 | 0.128 | 4.5% | 0.322 | 11.3% |

IMMULITE 2000 HBsAg Intrassay and Total Precision (ratio)

Site 1

| | | Intra-assay | | Total | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.55 | 0.060 | 11.1% | 0.074 | 13.6% |
| 2 | 0.53 | 0.042 | 7.8% | 0.061 | 11.4% |
| 3 | 1.16 | 0.091 | 7.8% | 0.098 | 8.4% |
| 4 | 1.20 | 0.074 | 6.2% | 0.177 | 14.8% |
| 5 | 1.47 | 0.102 | 7.0% | 0.214 | 14.6% |
| 6 | 2.56 | 0.149 | 5.8% | 0.243 | 9.5% |

Site 2

| | | Intra-assay | | Total | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.46 | 0.041 | 8.9% | 0.052 | 11.2% |
| 2 | 0.48 | 0.059 | 12.0% | 0.066 | 13.7% |
| 3 | 1.18 | 0.063 | 5.4% | 0.093 | 7.9% |
| 4 | 1.18 | 0.059 | 5.0% | 0.152 | 12.9% |
| 5 | 1.45 | 0.092 | 6.4% | 0.161 | 11.1% |
| 6 | 2.80 | 0.149 | 5.3% | 0.244 | 8.7% |

Site 3

| | | Intra-assay | | Total | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.50 | 0.038 | 7.6% | 0.059 | 11.7% |
| 2 | 0.50 | 0.051 | 10.2% | 0.071 | 14.2% |
| 3 | 1.17 | 0.126 | 10.8% | 0.171 | 14.7% |
| 4 | 1.18 | 0.053 | 4.5% | 0.144 | 12.2% |
| 5 | 1.48 | 0.091 | 6.1% | 0.129 | 8.7% |
| 6 | 2.70 | 0.117 | 4.3% | 0.406 | 15.0% |

IMMULITE HBsAg Lot-to-Lot and Site-to-Site:

| | | Lot-to-Lot | | Site-to-Site | |
|---|---|---|---|---|---|
| | Mean | SD | CV | SD | CV |
| 1 | 0.47 | 0.062 | 13.2% | 0.063 | 13.4% |
| 2 | 0.47 | 0.069 | 14.7% | 0.069 | 14.9% |
| 3 | 1.17 | 0.095 | 8.1% | 0.099 | 8.5% |
| 4 | 1.19 | 0.157 | 13.2% | 0.165 | 13.8% |
| 5 | 1.50 | 0.181 | 12.1% | 0.182 | 12.1% |
| 6 | 2.85 | 0.266 | 9.3% | 0.273 | 9.6% |

IMMULITE 2000 HBsAg Site-to-Site Precision:

| | Site-to-Site | | |
|---|---|---|---|
| | Mean | SD | CV |
| 1 | 0.50 | 0.070 | 13.9% |
| 2 | 0.51 | 0.069 | 13.7% |
| 3 | 1.17 | 0.126 | 10.7% |
| 4 | 1.18 | 0.158 | 13.3% |
| 5 | 1.47 | 0.172 | 11.7% |
| 6 | 2.69 | 0.321 | 11.9% |

The IMMULITE 2000 HBsAg lot-to-lot precision was not evaluated on three lots**.** Because the reproducibility of the assay for lot-to-lot was previously established, and Stability studies were performed using three lots, and the data was acceptable, no additional reproducibility studies were required.

EDTA, heparin, and sodium citrate samples were assayed in duplicate in three runs on three days at three U.S. sites for three lots of IMMULITE HBsAg and one lot of IMMULITE 2000 HBsAg. The median total variance of coefficients (EDTA, 5.2%; heparin, 7.2%; sodium citrate, 5.9%) demonstrated that these alternative sample types do not affect the precision of IMMULITE HBsAg.

**Stability**

Stability studies for IMMULITE and IMMULITE 2000 HBsAg and HBsAg Confirmatory were conducted by using 3 lots of IMMULITE HBsAg and 3 lots of HBsAg Confirmatory, and one lot of IMMULITE 2000 HBsAg. The kits and components were subjected to different storage/stress conditions to simulate adverse conditions that might be encountered during shipment and use at clinical laboratories, to establish the long-term (shelf-life) claims, to approximate and support the real time stability and to test the robustness of individual components.

These studies demonstrated that the performance of IMMULITE HBsAg, IMMULITE 2000 HBsAg and IMMULITE HBsAg Confirmatory assays was not affected if properly stored at package insert conditions for at least 720 days.

These studies also demonstrated that the performance of IMMULITE HBsAg, IMMULITE 2000 HBsAg and IMMULITE HBsAg Confirmatory assays was not affected following initial stresses (37°C, or –20°C) for at least 720 days.

## IX. Summary of Clinical Studies

**Expected Values**

Individuals acutely infected with the hepatitis B virus will exhibit a rapid rise (normally peaks at 12 weeks) and decline of detectable levels of HBsAg between 1 and 4 months after exposure; usually through the course of the clinical illness. HBsAg in acute infection can be detected as early as 1 or 2 weeks and as late as 11 or 12 weeks. Of acutely infected adults, 5–10% will become chronic carriers of the virus. In chronic carriers, no significant decrease in HBsAg level is observed. Because of variation in individual acute patients and the timing, frequency and length of follow-up for each individual patient, the percentage of specimens reported with positive results can be very variable, as shown in the studies below.

Demographics and expected prevalence rates for different categories of subjects (apparently healthy individuals, HBV Chronic, HBV Acute patients) each of whom provided one specimen, from four clinical studies, one in the northwestern United States (Study 1), two in the southern United States (Study 3, using specimens from China, and Study 4) and one in Europe, are summarized in the package insert.

Five clinical studies were conducted to assess the performance of the IMMULITE HBsAg (total number of subjects = 3268) and IMMULITE 2000 HbsAg (total number of subjects = 2968) assays.

The participating subjects each contributed one specimen to the analyses. The specimens were tested by FDA-approved or licensed hepatitis B assays (Reference markers), IMMULITE HbsAg, and IMMULITE 2000 HbsAg. All specimens in the analyses were initial test results.

The data were analyzed following the assignment of specimen classification based upon the reactive(+)/ nonreactive(-) patterns for the HBV reference serological markers. Specimen classification was based only on the HBV serological marker results for that particular specimen. No other laboratory or clinical information was used in the disease classification process.

**Study 1:** Conducted in the northwestern United States, this study included 281 patients, consisting of 138 males and 88 females. Gender for 55 subjects was not reported. These subjects had an average age of 43 years, ranging from 21 to 85 years. Distributions of the ethnicity of the subjects are shown in the following table.

| Ethnicity | *N* | % |
|---|---|---|
| African American | 15 | 5.3% |
| Caucasian | 169 | 60.1% |
| Hispanic | 2 | 0.7% |
| Asian | 32 | 11.4% |
| Other | 3 | 1.1% |
| Unknown | 60 | 21.4% |
| Total | 281 | 100.0% |

These subjects included acute and chronic hepatitis B patients, vaccinated individuals, pregnant women, and apparently healthy individuals, and patients with potentially crossreactive substances and medical conditions.

A total of 281 specimens were prospectively (n=92) and retrospectively (n=189) collected and tested by FDA-approved or licensed hepatitis B assays for six HBV serological markers (HbsAg, HbeAg, Anti-HBc IgM, Anti-HBc, Anti-Hbe, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated 17 unique patterns:

| Characterization based on single point specimens | No. of patients | HBV Reference Markers | | | | | |
|---|---|---|---|---|---|---|---|
| | | HbsAg | HbeAg | Anti-HBc IgM | Anti-HBc | Anti-Hbe | Anti-HBs |
| Acute | 2 | + | – | – | – | – | – |
| Acute | 1 | + | + | – | – | – | – |
| Acute | 32 | + | – | +/- | + | + | – |
| Acute | 34 | + | + | +/- | + | – | – |
| Chronic | 2 | + | – | – | + | – | – |
| Chronic | 3 | + | +/- | – | + | + | + |
| Chronic | 1 | + | – | – | + | – | + |
| Chronic | 1 | + | + | +/- | + | – | + |
| Early Recovery | 16 | – | – | +/- | + | + | + |
| Early Recovery | 4 | – | – | – | + | + | – |
| Early Recovery | 19 | – | – | – | + | +/- | – |
| Early Recovery | 1 | – | – | + | + | +/- | + |
| HBV vaccine response | 27 | – | – | – | – | – | + |
| Not previously infected | 120 | – | – | – | – | – | – |
| Recovered | 16 | – | – | – | +/- | – | + |
| Recovered | 1 | – | +/- | – | + | – | + |
| Uninterpretable | 1 | – | + | – | – | – | – |

Based on the above classifications the IMMULITE and IMMULITE 2000 HbsAg results were compared to Kit A, a reference assay for the determination of HbsAg.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML HbsAg | | | | |
| | + | – | + | – | |
| HB Acute infection | 67 | 2 | 0 | 0 | 69 |
| HB Chronic infection | 7 | 0 | 0 | 0 | 7 |
| HB Early recovery | 0 | 0 | 0 | 40 | 40 |
| HBV Vaccine response | 0 | 0 | 0 | 27 | 27 |
| Not previously infected | 0 | 0 | 1 | 119 | 120 |
| Recovered | 0 | 0 | 1 | 16 | 17 |
| Uninterpretable | 0 | 0 | 0 | 1 | 1 |
| Total | 74 | 2 | 2 | 203 | 281 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement. The Total Positive agreement is 97.4% (74/76) 95% with 95% CI of 90.8 to 99.7%. The Negative agreement is 99.0% (203/205) with a 95% CI of 96.5 to 99.9%. The Total agreement is 98.6% (277/281) with a 95% CI of 96.4 to 99.6%. The complete data by category is presented in the package insert.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML 2000 HBsAg | | | | |
| | + | – | + | – | |
| HB Acute infection | 67 | 2 | 0 | 0 | 69 |
| HB Chronic infection | 7 | 0 | 0 | 0 | 7 |
| HB Early recovery | 0 | 0 | 2 | 38 | 40 |
| HBV Vaccine response | 0 | 0 | 0 | 27 | 27 |
| Not previously infected | 0 | 0 | 6 | 114 | 120 |
| Recovered | 0 | 0 | 1 | 16 | 17 |
| Uninterpretable | 0 | 0 | 0 | 1 | 1 |
| Total | 74 | 2 | 9 | 196 | 281 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement. The Total Positive agreement is 97.4% (74/76) with a 95% CI of 90.8 to 99.7%. The Negative agreement is 95.6% (196/205) with a 95% CI of 91.8 to 98.0%. The Total agreement is 96.1% (270/281) with a 95% CI of 93.1 to 98.0%. The complete data by category is presented in the package insert.

**Study 2:** Conducted in the northeastern United States, this study included 209 patients, consisting of 104 males and 103 females. Gender for two patients was not reported. These patients had an average age of 47 years, ranging from newborn to 93 years. Distributions of the ethnicity of the patients are shown in the following table.

| Ethnicity | *N* | % |
|---|---|---|
| African American | 21 | 10.0% |
| Caucasian | 101 | 48.3% |
| Hispanic | 3 | 1.4% |
| Asian | 6 | 2.9% |
| Other | 7 | 3.3% |
| Unknown | 71 | 34.0% |
| Total | 209 | 100.0% |

Included were patients with potentially crossreactive substances and medical conditions.

A total of 209 retrospective specimens were collected and tested by FDA-approved or licensed hepatitis B assays for four HBV serological markers (HBsAg, Anti-HBc IgM, Anti-HBc, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated eight unique patterns:

| Characterization based on single point specimens | Number of patients | HBV Reference Markers | | | |
|---|---|---|---|---|---|
| | | HBsAg | Anti-HBc IgM | Anti-HBc | Anti-HBs |
| Acute | 8 | + | – | – | – |
| Acute | 9 | + | +/- | + | – |
| Chronic | 2 | + | – | + | + |
| Early recovery | 33 | – | +/- | + | + |
| Early recovery | 17 | – | – | + | – |
| HBV vaccine response | 32 | – | – | – | + |
| Not previously infected | 107 | – | – | – | – |
| Uninterpretable | 1 | + | – | – | + |

Based on the above classifications the IMMULITE and IMMULITE 2000 HBsAg results were compared to Kit A.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML HBsAg | | | | |
| | + | – | + | – | |
| HB Acute infection | 12 | 5 | 0 | 0 | 17 |
| HB Chronic infection | 1 | 1 | 0 | 0 | 2 |
| HB Early recovery | 0 | 0 | 0 | 50 | 50 |
| HBV Vaccine response | 0 | 0 | 0 | 32 | 32 |
| Not previously infected | 0 | 0 | 2 | 105 | 107 |
| Uninterpretable | 1 | 0 | 0 | 0 | 1 |
| Total | 14 | 6 | 2 | 187 | 209 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement. Total Positive agreement is 70.0% (14/20) with a 95% CI of 45.7 to 88.1%. The Negative agreement is 98.9% (187/189) with 95% CI of 96.2 to 99.9%. Total agreement is 96.2% (201/209) with a 95% CI of 92.6 to 98.3%. The complete data by category is presented in the package insert.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML 2000 HBsAg | | | | |
| | + | – | + | – | |
| HB Acute infection | 11 | 6 | 0 | 0 | 17 |
| HB Chronic infection | 1 | 1 | 0 | 0 | 2 |
| HB Early recovery | 0 | 0 | 1 | 49 | 50 |
| HBV Vaccine response | 0 | 0 | 0 | 32 | 32 |
| Not previously infected | 0 | 0 | 1 | 106 | 107 |
| Uninterpretable | 1 | 0 | 0 | 0 | 1 |
| Total | 13 | 7 | 2 | 187 | 209 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement. The Total Positive Agreement is 65.0% (13/20) with a 95% CI of 40.8 to 84.6%. The Negative agreement is 98.9% (187/189) with a 95% CI of 96.2 to 99.9%. The Total agreement is 95.7% (200/209) with a 95% CI of 92.0 to 98.0%. The complete data by category is presented in the package insert.

**Study 3:** Specimens obtained from China were tested in the southern United States and were comprised of 13 females and 55 males (gender for 11 patients was not reported) with an average age of 36 years, ranging from 18 to 82 years. These were prospectively recruited patients from a clinically well-characterized, homogeneous population: acute hepatitis B patients who presented with symptoms typical of acute hepatitis B such as jaundice, persistent fatigue, loss of appetite, pale stools and liver enlargement. Their ALT and AST results were significantly elevated at the time of diagnosis.

A total of 79 specimens were prospectively collected and tested by FDA-approved or licensed hepatitis B assays for six HBV serological markers (HBsAg, HBeAg, Anti-HBc IgM, Anti-HBc, Anti-HBc, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated 11 unique patterns:

| Characterization based on single point specimens | Number of patients | HBV Reference Markers | | | | | |
|---|---|---|---|---|---|---|---|
| | | HBsAg | HBeAg | Anti-HBc IgM | Anti-HBc | Anti-HBe | Anti-HBs |
| Acute | 23 | + | – | +/- | + | + | – |
| Acute | 8 | + | +/- | + | + | + | – |
| Acute | 1 | + | – | + | +/- | – | – |
| Acute | 35 | + | + | +/- | + | – | – |
| Acute | 4 | + | + | + | + | – | +/- |
| Chronic | 1 | + | – | – | + | – | – |
| Chronic | 3 | + | +/- | – | + | + | – |
| Chronic | 1 | + | + | +/- | + | – | + |
| Chronic | 1 | + | + | + | + | + | + |
| Recovered | 1 | – | – | – | +/- | – | + |
| Uninterpretable | 1 | + | – | + | + | + | + |

Based on the above classifications the IMMULITE and IMMULITE 2000 HBsAg results were compared to Kit A.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML HBsAg | | | | |
| | + | – | + | – | |
| HB Acute infection | 70 | 1 | 0 | 0 | 71 |
| HB Chronic infection | 6 | 0 | 0 | 0 | 6 |
| Recovered | 0 | 0 | 0 | 1 | 1 |
| Uninterpretable | 1 | 0 | 0 | 0 | 1 |
| Total | 77 | 1 | 0 | 1 | 79 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement. The Total Positive agreement is 98.7% (77/78) with a 95% CI of 93.1 to 100.0%. There was only 1 negative sample, so Negative agreement could not be calculated. The Total agreement is 98.7% (78/79) with a 95% CI of 93.1 to 100.0% The complete data by category is presented in the package insert.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML 2000 HBsAg | | | | |
| | + | – | + | – | |
| HB Acute infection | 71 | 0 | 0 | 0 | 71 |
| HB Chronic infection | 6 | 0 | 0 | 0 | 6 |
| Recovered | 0 | 0 | 0 | 1 | 1 |
| Uninterpretable | 1 | 0 | 0 | 0 | 1 |
| Total | 78 | 0 | 0 | 1 | 79 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement. The Total Positive agreement is 98.7% (78/79) with a 95% CI of 93.1 to 100.0%. The complete data by category is presented in the package insert.

**Study 4:** Conducted in the southern United States, this study included retrospectively collected specimens from 200 pregnant subjects. These subjects had an average age of 28 years, ranging from 17 to 41 years.

A total of 200 specimens were tested by FDA-approved or licensed hepatitis B assays for four HBV serological markers (HBsAg, Anti-HBc IgM, Anti-HBc, and Anti-HBs). Characterization based on single point specimens by the reference serological markers demonstrated three unique patterns:

| Characterization based on single point specimens | Number of subjects | HBV Reference Markers | | | |
|---|---|---|---|---|---|
| | | HBsAg | Anti-HBc IgM | Anti-HBc | Anti-HBs |
| Early recovery | 4 | – | +/- | + | + |
| Early recovery | 2 | – | – | + | – |
| HBV vaccine response | 42 | – | – | – | + |
| Not previously infected | 152* | – | – | – | – |

Based on the above classifications the IMMULITE and IMMULITE 2000 HBsAg results were compared to Kit A.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML HBsAg | | | | |
| | + | – | + | – | |
| Early recovery | 0 | 0 | 0 | 6 | 6 |
| HBV vaccine response | 0 | 0 | 0 | 42 | 42 |
| Not previously infected | 0 | 0 | 1 | 148 | 149* |
| Total | 0 | 0 | 1 | 196 | 197 |

* Three specimens were not tested for IMMULITE HBsAg.

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement or Total Positive agreement. The Total Negative agreement is 99.5% (196/197) with a 95% CI of 97.2 to 100.0%. The complete data by category is presented in the package insert.

| Reference Serological Characterization | Kit A | | | | Total |
|---|---|---|---|---|---|
| | + | | – | | |
| | IML 2000 HBsAg | | | | |
| | + | – | + | – | |
| Early recovery | 0 | 0 | 0 | 6 | 6 |
| HBV vaccine response | 0 | 0 | 0 | 42 | 42 |
| Not previously infected | 0 | 0 | 0 | 152 | 152 |
| Total | 0 | 0 | 0 | 200 | 200 |

There was insufficient numbers for each category of subjects to determine Negative and Positive Agreement or Total Positive agreement. The Total Negative agreement is 100.0% (200/200) with a 95% CI of 98.2 to 100.0%. The complete data by category is presented in the package insert.

**Study 5:** In a clinical study conducted in Europe, IMMULITE and IMMULITE 2000 HBsAg was compared to Kit B, a commercially available HBsAg electro-chemiluminescence immunoassay. Presented below are the comparisons between IMMULITE HBsAg, IMMULITE 2000 HBsAg and Kit B (one specimen per subject).

| Kit B | | | | |
|---|---|---|---|---|
| + | | – | | |
| IML HBsAg | | | | |
| + | – | + | – | Total |
| 412 | 12 | 26 | 2049 | 2499 |

Positive agreement = 97.2% (412/424)
95% CI = 95.1 to 98.5%
Negative agreement = 98.7% (2049/2075)
95% CI = 98.2 to 99.2%
Total agreement = 98.5% (2461/2499)
95% CI = 97.9 to 98.9%

| Kit B | | | | |
|---|---|---|---|---|
| + | | – | | |
| IML 2000 HBsAg | | | | |
| + | – | + | – | Total |
| 118 | 12 | 15 | 2054 | 2199 |

Positive agreement = 90.8% (118/130)
95% CI = 84.4 to 95.1%
Negative agreement = 98.0% (2054/2096)
95% CI = 97.3 to 98.6%
Total agreement = 98.8% (2172/2199)
95% CI = 98.2 to 99.2%

**IMMULITE HBsAg Confirmatory**

In a European study, specimens with positive HBsAg results by IMMULITE HBsAg were further tested by the IMMULITE HBsAg Confirmatory procedure. The results are shown in the following table.

| Specimens | HBsAg Confirmatory |
|---|---|
| 273 positive by IMMULITE HBsAg | 267 confirmed positive |
| | 6 not confirmed* |

* The 6 specimens not confirmed all had extremely high counts (CPS). Further dilution of these specimens (not done) would probably have confirmed the positivity of these specimens.

In one clinical study in the United States, 200 specimens from apparently healthy pregnant women with an average age of 28 years were tested by the IMMULITE 2000 HBsAg assay, Kit A, and the IMMULITE HBsAg Confirmatory procedure. The results are shown in the following table.

| Specimens | HBsAg Confirmatory |
|---|---|
| 200 negative by IMMULITE 2000 HBsAg and Kit A | 200 not confirmed positive |

In two other clinical studies in the United States, test results of 19 specimens (6 females, 13 males, with an average age of 47 years) were found to be discordant either between IMMULITE HBsAg and a commercially available HBsAg assay (Kit A), or between IMMULITE 2000 HBsAg and Kit A. These specimens were retested by all three assays and the IMMULITE HBsAg Confirmatory procedure. The results are shown in the following table.

| Specimens | Final Determination* | HBsAg Confirmatory |
|---|---|---|
| 19 specimens with discordant HBsAg results | 17 negative | 17 not confirmed positive |
| | 2 positive | 1 not confirmed positive |
| | | 1 confirmed positive |

* Negative if 2/3 or 3/3 results were negative. Positive if 2/3 or 3/3 results were positive.

In an additional study conducted in-house, 38 specimens that had tested positive by IMMULITE HBsAg were further tested by the IMMULITE HBsAg Confirmatory procedure and a commercially available HBsAg Confirmatory assay (Kit A).

| Kit A | | | | |
|---|---|---|---|---|
| + | | – | | |
| IML HBsAg Confirmatory | | | | |
| + | – | + | – | Total |
| 37 | 0 | 1* | 0 | 38 |

Positive agreement = 100.0% (37/37)
95% CI = 90.5 to 100.0%
Negative agreement = N/A (0/1)
95% CI = N/A
Total agreement = 97.4% (37/38)
95% CI = 86.2 to 99.9%

* This specimen had a signal reduction of 59% by IMMULITE HBsAg Confirmatory and 48% by Kit A.

Performance with Plasma Specimens

In a study conducted in the northwestern United States, blood specimens from 18 chronic hepatitis B patients at different stages of the disease were drawn into plain, heparinized, sodium citrate and EDTA vacutainer tubes. All serum and all plasma specimens were tested by IMMULITE HBsAg and IMMULITE 2000 HBsAg. Positive results were further tested by IMMULITE HBsAg Confirmatory and all were conformed positive.

| Specimens | IML HBsAg Results | IML 2000 HBsAg Results | HBsAg Confirmatory |
|---|---|---|---|
| 18 Serum | 17/18 positive | 17/18 positive | All 17 Confirmed |
| 18 Heparinized | 17/18 positive | 17/18 positive | All 17 Confirmed |
| 18 Sodium citrate | 17/18 positive | 17/18 positive | All 17 Confirmed |
| 18 EDTA | 17/18 positive | 17/18 positive | All 17 Confirmed |

## X. CONCLUSIONS DRAWN FROM STUDIES

The data from both the non-clinical and clinical studies demonstrate that acceptable performance is obtained with the IMMULITE HBsAg, IMMULITE 2000 HBsAg and IMMULITE HBsAg Confirmatory assays to detect hepatitis B surface antigen in human serum or plasma.

### Safety

As a diagnostic test, the IMMULITE HBsAg, IMMULITE 2000 HBsAg and IMMULITE HBsAg Confirmatory assays involve removal of blood from an individual for testing purposes. The test, therefore, presents no more safety hazard to an individual being tested than other tests where blood is removed.

### Benefit/Risks

The submitted clinical studies have shown that the IMMULITE HBsAg, IMMULITE 2000 HBsAg and IMMULITE HBsAg Confirmatory assays, when compared to reference clinical laboratory procedures, have a similar ability to detect the presence of HBsAg in specimens from individuals acutely and chronically infected with HBV. The rate of false positivity and false negativity are within acceptable limits compared to the reference assay. It has been shown that the device has no demonstrable cross-reactivity with other viruses or organisms that may cause clinical hepatitis. Therefore, these devices should benefit the physician in the diagnosis of HBV.

Based on the results of the preclinical and clinical laboratory studies the IMMULITE HBsAg, IMMULITE 2000 HBsAg and IMMULITE HBsAg Confirmatory assays, when used according to the provided directions and in conjunction with other serological and clinical information, should be safe and effective and pose minimal risk to the patient due to false test results.

## XI. PANEL RECOMMENDATION

Pursuant to Section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Microbiology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.

## XII. CDRH DECISION

The applicant's manufacturing facility was found to be in compliance with the Quality Systems Regulation (21 CFR 820). FDA issued an approval order on July 26, 2002.

## XIII. APPROVAL SPECIFICATIONS

Directions for Use: See labeling

Hazards to Health from Use of the Device: See Contraindications, Warnings, Precautions and Adverse Events in the labeling**.**

Postapproval Requirements and Restrictions: See approval order.